

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-902**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use**

NDA NUMBER

NDA 21-902

NAME OF APPLICANT / NDA HOLDER

MediGene AG

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

Polyphenon® E Ointment, 15%

ACTIVE INGREDIENT(S)

green tea extract, Polyphenon® E

STRENGTH(S)

15% w/w

DOSAGE FORM

Ointment

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,795,911

b. Issue Date of Patent

8/18/1998

c. Expiration Date of Patent

10/4/2017

d. Name of Patent Owner

Mitsui Norin Co., Ltd.

Address (of Patent Owner)

3-2-11, Nishishinjuku, Shinjuku-ku

City/State

Tokyo

ZIP Code

160-8381 Japan

FAX Number (if available)

+81-03-5510-2551

Telephone Number

+81-03-3539-6501

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

600 Congress Avenue, Suite 2400

City/State

Austin, Texas

ZIP Code

78701-2978

FAX Number (if available)

(512) 536-4598

Telephone Number

(512) 474-5201

E-Mail Address (if available)

David L. Parker

Albright & Jaworski L.L.P.

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**Drug Substance (Active Ingredient)**

Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 1-3, 5-7, 11 and 14	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) The subject claims are directed to topical treatment of external genital and perianal warts (Condylomata acuminata)	

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



August 24, 2005

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
MediGene AG

Address  
Lochhamer Strasse 11

City/State  
Planegg/Martinsried

ZIP Code  
82152 Germany

Telephone Number  
+49-89-8565-290

FAX Number (if available)  
+49-89-8565-2920

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## INFORMATION AND INSTRUCTIONS FOR FORM 3542a

### PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

#### General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

##### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

##### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

##### 4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

##### 5. No Relevant Patents

Complete this section only if applicable.

##### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**additional page to Form FDA 3542a (7/03)**

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re 1.d.: Second patent owner

Name of Second Patent Owner

Cancer Institute (Hospital) Chinese Academy of Medical Sciences

Address (of Second Patent Owner)

Panjiayuan No. 17

City/State

Chaoyang District, Beijing

ZIP Code

100021 China

Appears This Way  
On Original

## EXCLUSIVITY SUMMARY

NDA # 21-902

SUPPL # N/A

HFD # 540

Trade Name Veregen Ointment, 15%

Generic Name kunecatechins (Going to be changed later. USAN and Sponsor did not reach agreement this review cycle.

Applicant Name MediGene, Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1 !  
! YES  ! NO   
! Explain: ! Explain:

Investigation #2 !  
! YES  ! NO   
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Millie Wright  
Title: Project Manager  
Date: October 11, 2006

Name of Office/Division Director signing form: Susan Walker. M.D.  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Susan Walker  
10/13/2006 01:35:43 PM

## Claimed Exclusivity

**NDA 21-902:** Polyphenon<sup>®</sup> E Ointment, 15%

**Applicant:** MediGene AG  
Lochhamer Str. 11  
D-82152 Planegg/Martinsried  
Germany

**Indication:** External genital and perianal warts

Pursuant to 21 CFR § 314.50(j), MediGene AG claims five year exclusivity for Polyphenon<sup>®</sup> E Ointment. Polyphenon<sup>®</sup> E Ointment, which contains the active moiety Polyphenon<sup>®</sup> E is entitled to exclusivity under 21 CFR § 314.108(b)(2). The active moiety Polyphenon<sup>®</sup> E is derived from tea leaves of *Camellia sinensis* and is a mixture of the following marker catechins: Epigallocatechin gallate (EGCg), Epigallocatechin (EGC), Epicatechin gallate (ECg), Epicatechin (EC), Gallocatechin gallate (GCg), Catechin gallate (Cg), Gallocatechin (GC), and Catechin (C). MediGene AG has reviewed FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, 25<sup>th</sup> Edition and Supplement through June 2005, and has found no approved drug that uses the active moiety Polyphenon<sup>®</sup> E or any of its marker catechins. Therefore, to the best of MediGene AG's knowledge, FDA has not approved a drug under section 505(b) that contains the active moiety or any marker catechins found in Polyphenon<sup>®</sup> E Ointment.

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## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # :21-902

Supplement Type (e.g. SE5):N/A

Supplement Number: N/A

Stamp Date: 9/30/05

PDUFA Goal Date: 10/31/06 (3 month extension)

HFD 540 Trade and generic names/dosage form Veregen (kunicatechins) Ointment, 15%

Applicant MediGene, Inc.

Therapeutic Class: 1S

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

Yes. Please proceed to the next section.

No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: For the topical treatment of external genital and perianal warts (condylomata acuminata) caused by the human papilloma virus in adult patients.

Is this an orphan indication? No

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: Veregen offers no meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients. Veregen was developed for the adult patient population. This is a sexually transmittable viral disease; therefore, the number of pediatric patients is limited. In the United States in 2004, there were only \_\_\_\_\_ prescriptions written for genital and perianal warts in the age group 0-16 according to IMS health database. As a therapeutic alternative, Aldara (imiquimod) is available in the U.S. market for the age group 12 years and above.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

NDA ##-###

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

**Millie Wright**

**Regulatory Project Manager**

**cc: NDA 21-902  
HFD-960/ Rosemary Addy or Grace Carmouze**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG  
DEVELOPMENT, HFD-960, 301-594-7337.**

**(revised 6-23-2005)**

**Appears This Way  
On Original**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-902  
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 6-23-2005)

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Susan Walker  
10/20/2006 04:26:24 PM

## Debarment Certification

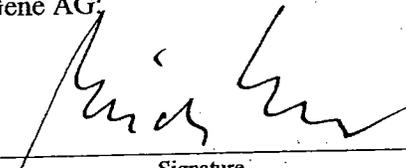
**NDA 21-902:** Polyphenon® E Ointment, 15%

**Applicant:** MediGene AG  
Lochhamer Str. 11  
D-82152 Planegg/Martinsried  
Germany

**Indication:** External genital and perianal warts

MediGene AG hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

MediGene AG:

  
\_\_\_\_\_  
Signature  
Dr. U. Delvos, Head R&D  
\_\_\_\_\_  
Name, Title  
August 3<sup>rd</sup>, 2005  
\_\_\_\_\_  
Date

MediGene, Inc.:  
(U.S. Representative)

  
\_\_\_\_\_  
Signature  
Pam Larson, Sr. Manager Reg. Affairs  
\_\_\_\_\_  
Name, Title  
August 8, 2005  
\_\_\_\_\_  
Date

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**NDA 21902-00**

**October 31, 2006**

**MEMO TO FILE**

**Clinical Reviewer: Elektra Papadopoulos, M.D.**

**Clinical Team Leader: Jill Lindstrom, M.D.**

The sponsor agreed on October 30, 2006 to a modification of the indication section of the package insert as follows.

Veregen<sup>TM</sup> is indicated for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) \_\_\_\_\_ in immunocompetent patients 18 years and older.

The diagnosis of condyloma acuminata was a clinical diagnosis in the clinical trials supporting licensure. Since no biopsies for histopathology or viral typing were performed, the Agency has proposed deleting \_\_\_\_\_ from the indication section. The rationale given at the internal labeling meeting for accepting the original statement \_\_\_\_\_ was to avoid any possible confusion with condyloma latum, a form of secondary syphilis caused by *Treponema pallidum* and in the differential diagnosis of condyloma acuminata.

Since the clinical trials excluded subjects who were known to be immunosuppressed, the indication statement now reads "in immunocompetent patients 18 years and older". There is also a precaution stating that no studies have been done in immunocompromised patients and this statement was previously agreed to by the sponsor. A similar statement under the precautions section is found in other approved products for external genital and perianal warts.

**Division Director Memorandum  
Dermatology and Dental Products**

NDA: 21-902/000

Drug: Veregen 15% Ointment

Indication: Veregen™ is indicated for the topical treatment of external genital and perianal warts (*Condyloma acuminata*) caused by the human papilloma virus in patients 18 years and older

Dose: Topical treatment three times daily for up to 16 weeks

Applicant: MediGene, Inc.

Submission Received: 30Sept05

PDUFA Date: 31Oct06

Date of Memorandum: 28Oct06

---

**SUMMARY**

The applicant has requested approval for Veregen, a new molecular entity for the treatment of condyloma acuminata. The drug substance in this botanical drug product is a mixture of chemical species (catechins and other related compounds) originating from the leaves of green tea (*Camellia sinensis* (L.) O.Kuntze).

This is the first new drug application for a botanical product since the drafting of the botanical guidance. Several novel and unique issues, both scientific and regulatory, were considered during the team review. These included how to adequately demonstrate identification and control of the botanical raw material, how to demonstrate adequate characterization of the drug substance, how to ensure the therapeutic consistency of marketing batches, how to name the drug substance, and how to evaluate the pharmacodynamics/kinetics for a product with multiple active ingredients. Each of these issues was addressed and resolved adequately by the review team for this drug product.

In support of safety and efficacy for this indication the sponsor has submitted clinical study data from two randomized, placebo controlled phase 3 trials, CT1017 and CT1018, in which the primary endpoint was complete clearance of all baseline and new lesions of condyloma acuminata (genital warts) by week 16 of treatment. Study subjects applied a thin film of the drug product three times daily until resolution of the lesions. These studies demonstrated success for the primary endpoint but the applicant did not provide adequate information on follow-up/recurrence to inform labeling. Approximately 1,000

patients participated in the Phase 3 trials, primarily outside the United States. The safety profile was considered acceptable.

I am in agreement with the recommendations of the primary reviewers that this application should be approved. Phase 4 commitments should address the clinical pharmacology issues.

## **KEY ISSUES**

### **Botanical/Chemistry, manufacturing, controls**

#### **Control of the drug substance**

Botanical drug substances are multi-component mixtures, subject to variations in quality and quantity of components arising from changes in the raw materials or manufacturing processes. To ensure consistency and quality of the drug substance, the starting raw material must be adequately identified, with control of the location, growing conditions, and harvesting methods for the plant. The manufacturing process which converts the raw materials into the final drug substance must be controlled so that the level of the individual components in the multi-component mixture is consistent between batches. Because of these unique compositional factors, botanical substances are not necessarily amenable to the same characterization methodologies as the usual synthetic small single molecule drug substances. The two critical steps of raw materials control and manufacturing control were addressed by the botanical and CMC reviewers.

#### **Raw Materials Control:**

The botanical review team worked with the sponsor to ensure that the tea variety/cultivars for *Camellia sinensis* (L.) O. Kuntze were identified and controlled in the to-be-marketed product. Significant variation in catechins and other chemical components have been identified from the tea leaves of different varieties/cultivars. The active ingredient in this drug substance is not identified, and the entire drug substance is determined to be the active. In order to ensure the therapeutic efficacy of individual and future batches of the drug substance, the NDA review team collaboratively determined that using the established cultivars from the drug development program would be important for maintaining consistency of the botanical raw material and the botanical drug substance. Any introduction of new varieties/cultivars should be pre-approved by the agency before production of marketing batches, and agency review/approval is needed for changing the suppliers of botanical raw materials.

The botanical reviewer recommends that International or local GAP (e.g., WHO Guidances on Good Agricultural and Collection Practices (GACP) for Medicinal Plants; GAP for Traditional Chinese Medicine, People's Republic of China) procedures for medicinal plants are to be followed in addition to the tea growing guidelines issued by the local authority for tea production for food/beverage uses, as appropriate. Through proper raw material control and manufacturing controls and specifications, drug product and

clinical effect consistency is expected to be met with no major practical difficulties. As there is no independent biological assay available to estimate the activity of the drug substance, acceptance criteria for this drug substance are designed to reflect the clinical batches used to demonstrate safety and efficacy. Extensive discussion occurred, and agreement was reached, between the sponsor and the agency regarding the allowable specification profile for the to-be-marketed formulation. The approval of this application includes agreements by the sponsor to comply with the raw materials, processing, and manufacturing controls agreed upon during the review process. *I concur with the recommendation of the NDA review team that any deviation from the specifications for the drug substance used in the trials to support the NDA would require additional clinical studies with the new drug substance.*

### Manufacturing Controls

Regulatory challenges for the first botanical NDA included characterization of the drug substance, ensuring batch-to-batch consistency (acceptance criteria), and naming of the drug substance.

**Characterization:** The drug substance specifications consist of: distinct assay and identification specifications which give the whole: Catechins, (85-95%); Related substances (2.5%) which includes caffeine, theobromine and gallic acid; and tea-related components (10%). HPLC methods are used to determine both the assay values of these components and the identification by fingerprinting.

A total of 8 catechins are identified and quantitated in the drug product.

**Batch-to-batch consistency:** Batch-to-batch consistency is addressed extensively in the CMC review. Qualitative is not performed either by the drug substance manufacturer or drug product manufacturer, therefore, the amounts of each catechin varies from lot to lot used to manufacture the drug product. Although botanicals are not defined as combination products, each ingredient is being considered active and must be controlled to show a pharmaceutical equivalency, if possible, as if it is an individual active molecule. To determine how to control the amount of each component, data analysis was performed by FDA and acceptance criteria were proposed based on the amounts contained in clinical batches which were determined to be efficacious. An in house analysis of the drug substance batches used in the drug product batches for clinical trials and stability was performed and an acceptance criterion for individual catechins, total catechins and other unidentified components of drug substance

was proposed. Agreement on these criteria is documented via an amendment on 04-OCT-06. The acceptance criterion of particle size of drug substance has also been included in the drug substance specifications via an amendment dated 28-SEP-2006.

There was an *extensive* communication between the applicant and FDA on the subject of acceptance criteria. The fundamental concept is that acceptance criteria for the drug substance batches are linked to demonstration of clinical efficacy via the clinical trials presented in the application.

The drug product is an ointment containing 15% (w/w) Kunecatechins drug substance suspended in a \_\_\_\_\_ n base. Excipients are isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate (also known as propylene glycol monopalmitostearate), and oleyl alcohol. Oleyl alcohol is identified \_\_\_\_\_ in this formulation.

the FDA recommends that prior to dispensing to the patient, the drug product needs to be stored at

refrigerated temperature [2<sup>0</sup>C to 8<sup>0</sup>C (36<sup>0</sup>F to 46<sup>0</sup>F)]. After dispensing to the consumer, consumer should not store the drug product above 25<sup>0</sup>C (77<sup>0</sup>F).

*The CMC reviewer has determined that the application may be approved from a CMC standpoint, and there are no Phase 4 recommendations.*

*The botanical reviewer concludes that there are no Botanical Review Team issues identified that may affect the approvability of the product.*

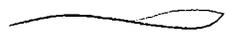
#### **Pharmacology/Toxicology:**

Veregen 15% Ointment or Kune catechin drug substance was tested for up to 3 months orally or topically in rats and dogs and for up to 9 months topically in mini-pigs. Gastrointestinal tract, liver, pancreas and lymphoid tissues were primarily affected in rats following oral administration. No apparent systemic toxicity was noted in mini-pigs after topical treatment of Veregen 15% Ointment for 9 months. Veregen Ointment induced minimal to severe local irritation including erythema, edema, and inflammatory reactions when topically applied to rats, rabbits, and mini-pigs. Veregen Ointment caused strong local irritation to vaginal mucosa after vaginal application in female rats and mini-pigs.

*The pharmacology/toxicology reviewer has determined that the application is approvable and there are not phase 4 recommendations.*

#### **Clinical Pharmacology:**

The applicant did not provide any information on what compounds in their drug product contribute to the safety and efficacy. As this is a botanical drug product, the entire drug substance is considered to be active.



The clinical pharmacology reviewer concludes that the totality of the data provided (i.e. nonclinical findings, clinical pharmacology and clinical trial data) suggested that the systemic exposure of the four major catechins following topical administration of Veregen Ointment, 15 % was minimal. The reviewer supports this conclusion with the observations that the clinical safety data indicate a low incidence of adverse events other than local reactions, and the nonclinical findings indicate that there was no apparent systemic toxicity noted in minipigs after topical treatment with Veregen Ointment, 15 %.

The assessment of the systemic exposure had to rely on the nonclinical and clinical safety data because the results obtained in the pharmacokinetic study # CT 1007 on the systemic exposure of the four major catechins (EGCg, EGC, ECg and EC) in Veregen Ointment, 15 % could not be interpreted. This was an open label comparative assessment of the pharmacokinetics of repeated topical application of Veregen ointment, 15% (3 times daily for 3 weeks) with a single oral intake of 400mL of brewed green tea. The plasma

samples were measured on day 1, 3, 14 and 21 in the topical arm. This study suggested that the systemic exposure to the four most abundant catechins in green tea extract may be minimal following topical application, however, the data are potentially flawed. In this study the samples were stored for an extended period of time before they were analyzed, and the plasma concentrations of the catechins may have degraded. Although the analytical method used to assay the four catechins in plasma was validated for sensitivity, accuracy, and precision, the long term stability evaluation to cover the period of sample collection to sample analyses (117 days to 354 days for the first patient) did not meet the acceptance criteria.

*The clinical pharmacology reviewer recommends that the data is acceptable and that the application is approvable.*

### **Clinical and Biostatistical Reviews:**

A total of 1085 patients with *condyloma acuminata* received a formulation of Veregen, either cream or ointment. Of the 1085 patients, 479 were treated with Veregen 10% ointment or cream and 606 patients were treated with Veregen 15% ointment. Another 47 patients were treated with an active comparator and 322 were treated with placebo. The safety population of the phase 2 and 3 randomized, placebo-controlled clinical studies of Veregen ointment three times daily included 400 patients receiving Veregen 10% ointment, 515 patients receiving Veregen 15% ointment and 247 patients receiving placebo.

The two phase 3 trials were studies CT 1017 and CT 1018. Both trials were similar in study design and sample size. Each trial consisted of a 16-week treatment period and a treatment free-period of 12-weeks to assess for recurring warts for those patients who had complete clearance of all warts. Clinical response in each trial was defined as complete clearance of all warts, baseline and new, by week 16. Treatment groups consisted of 15% Ointment, 10% Ointment and Vehicle in a randomization ratio of 2:2:1 in both trials. The prespecified primary analysis method was also the same in both trials, Fisher's exact test imputing missing data as the last observation carried forward (LOCF). Each of the two pivotal trials succeeded in demonstrating statistically significant treatment effect for both doses of active study drug compared with Vehicle using the pre-specified primary endpoints. Approximately 51% of patients treated with the 15% ointment in study CT1017 achieved success compared to 37% for vehicle, with statistical significance at 0.02. Approximately 57% of patients treated with 15% ointment in study CT1018 reached success compared to 34% for vehicle, with statistical significance at <0.001.

The new drug application seeks approval for the marketing of the 15% Ointment formulation. This formulation demonstrated a trend towards a higher treatment effect which was observed in both of the controlled clinical trials. There is no evidence to indicate that there is a greater clinical safety concern with the 15% product compared to the 10% product.

The adverse events seen in the clinical trials for Veregen were local in nature and consistent with those seen with other treatments for this condition. Patients should be followed by their physician during treatment and in cases where the use of the product causes severe reactions these are local in nature and can be readily recognized and managed. There is no evidence in clinical trials of Veregen of any systemic toxicity in association with the use of this product as labeled.

One significant issue discussed by the clinical reviewer is the absence of adequate information during the follow-up period. Given the possibility that anogenital warts may recur and new lesions may develop, data regarding recurrence rates may be useful for labeling. Although treatment responders in both pivotal phase 3 trials were to enter a 12-week follow-up period to assess for recurrence, the method of recording data in these studies made it impossible to estimate recurrence rates after treatment because the sponsor recorded both missing data and zero count data in the same way. As a result, it was not possible to distinguish whether a subject failed to appear for follow-up evaluation or did appear for the evaluation and had no warts. The sponsor has not provided data to inform accurate labeling regarding recurrence of lesions and this is reflected in the labeling statements in the PPI. Adequate data from appropriately designed trials would be needed prior to any labeling revisions.

*The biostatistical and clinical reviewers recommend approval of the 15% Ointment with labeling revisions.*

**Conclusion:**

Veregen Ointment 15% should be approved for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

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Susan Walker  
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DIRECTOR

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OCT 30 2006  
OUTREACH CENTER

US  
*[Handwritten signature]*

MediGene

MediGene, Inc.  
10660 Scripps Ranch Blvd., Suite 200  
San Diego, CA 92131 USA  
Tel. (858) 586-2240  
Fax (858) 586-2241  
www.medigene.com

October 26, 2006

Dr. Susan Walker  
Director  
Division of Dermatologic and Dental Products (HFD-540)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705

RECEIVED  
OCT 30 2006  
HFD-540/CDER  
ORIG AMENDMENT  
N-000-45

**RE: New Drug Application # 21-902**  
**Polyphenon® E Ointment, 15%**  
**Submission No. 047**  
**General Correspondence: MediGene's Agreement to Phase 4 Commitment (PK Study)**

Dear Dr. Walker:

This submission is in response to the Agency's approval of the draft proposal entitled "MediGene Phase 4 Post-Marketing Commitment Draft Proposal for Study 2" that was provided to the Agency via email on October 25, 2006. As requested by Millie Wright, FDA Project Manager, MediGene hereby acknowledges our agreement to the following Phase 4 Commitment:

**Study 2: Pharmacokinetic Study**

MediGene proposes a pharmacokinetic study comparing the catechin blood levels after drinking of green tea with those after topical application of Polyphenon® E Ointment, 15%. The two-arm study will be designed to enroll into one arm 20 evaluable patients ("completers") with external genital and perianal warts who will be treated 3 times daily for 7 days with Polyphenon® E Ointment, 15%, and into the second arm 20 evaluable healthy volunteers, who are to drink a green tea solution 3 times daily for 7 days. Blood samples for the analysis of catechin levels will be obtained prior to and at several sampling time points (over 12 hours) after oral intake of a green tea solution or topical application of Polyphenon® E Ointment, 15%, respectively, at Days 1 and 7. The study will be carried out

with material from the final commercial source for API to be established in Japan and fulfilling the FDA-defined specifications for the botanical drug substance and drug product.

Protocol Submission: by Jul 2007  
Study Start: by Jan 2008  
Final Report Submission: by Jan 2009

Reference is made to the FDA fax memorandum entitled "Post-marketing Studies (Phase 4s)" dated October 16, 2006. Reference is also made to MediGene's draft proposal entitled "MediGene Draft Proposal for Post-Marketing Phase 4 Studies" submitted to FDA on October 23, 2006 via email.

Four copies of this submission are provided as outlined below.

- Archive copy – blue vinyl binder
- Clinical copy – tan binder
- Clinical Pharmacology copy – orange binder
- Statistical copy – green binder

If there are any questions regarding this submission or if additional information is needed, please do not hesitate to contact me at (858) 586-2252 or by email at [p.larson@medigeneusa.com](mailto:p.larson@medigeneusa.com).

Sincerely,



Pam Larson  
Sr. Manager, Regulatory Affairs, US  
MediGene, Inc.

cc: Millie Wright, FDA Project Manager DDDDP (email)

NDA 21-902

MediGene Inc.

Attention: Myleen Ignacio, M.S., Regulatory Affairs Associate  
10660 Scripps Ranch Blvd., Suite 200  
San Diego, California 92131

Dear Ms. Ignacio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veregen (kunecatechins) Ointment, 15%.

We also refer to the teleconference between representatives of your firm and the FDA on September 21, 2006. The purpose of the teleconference was to discuss the drug product specifications and the drug substance specifications.

The official minutes of that teleconference are enclosed.

If you have any questions, call Millie Wright, Project Manager, at (301) 796-2110.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, M.D.

Dermatology Team Leader

Division of Dermatology and Dental Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Enclosure

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# MEMORANDUM OF TELECON

**DATE:** September 21, 2006

**Application:** NDA 21-902/ Veregen (kunecatechins) Ointment, 15%

**Sponsor:** MediGene, Inc.

**Topic:** Sponsor's submission dated September 14, 2006

**FDA Participants:**

**Division Dermatologic and Dental Drug Products/**

Jill Lindstrom, M.D., Dermatology Team Leader<sup>2</sup>

Millie Wright, RN, MSN, Project Manager

**Office of New Drug Quality Assessment II/Division of Pre-Marketing Assessment**

Moo-Jhong Rhee, Ph.D., Branch Chief

Rajiv Agarwal, M.Phil; Ph.D., Ph.D., Reviewing Chemist

**Sponsor Participants:**

Axel Mescheder, MD., Vice President .Clinical Research and Development

Annette Hüttig, Ph.D., Polyphenon<sup>®</sup> E Project Manager

Myleen Ignacio, M.S., Regulatory Affairs Associate II U.S.

K. Jon Kowal, Ph.D., Senior Vice President Research and Development

Paula Stemler, M.S., Director of Manufacturing Operations

Klaus Drexler, Ph.D., Senior Director CMC Chemicals

Irene Gander-Meisterernst, PhD, Senior Director, Regulatory Affairs, EU

**Background**

The Sponsor's submission, dated September 14, 2006 (see Attachment) was in response to a September 8, 2006 teleconference with the Agency.

The Sponsor requested that if the Agency did not agree with their proposal that they be notified immediately. The September 21, 2006 teleconference was scheduled to discuss their proposals.

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**Discussion:**

Dr. Lindstrom noted that the Sponsor is proposing a new drug product and drug substance specifications using the data from Study CT 1005. The proposal to use the data from Study CT 1005 is not acceptable to the Agency for the following reasons:

1. Study CT 1005 had a different study design.
2. The specification range in Study CT 1005 is higher than those used in the phase 3 pivotal trials.
3. The specifications need to be based on batches used in the pivotal phase 3 clinical trials. It was noted that the concern was more of a safety concern than an issue of efficacy.

The Sponsor was reminded that the time left in this review cycle was limited. Therefore, an agreement needs to be reached. The specifications proposed by the Agency are the only ones that are acceptable for a potential approval within this review cycle. The Sponsor agreed to the specifications proposed by the Agency.

Dr. Agarwal inquired about the pending specifications of the particle size of drug product. The applicant stated that the requested information will be submitted no later than the end of next week.

The applicant asked the FDA's rationale used to establish the drug substance specification. Dr. Agarwal stated that small individual drug substance batches were pooled together to manufacture a drug product batch. The pooled drug substance was not tested before it is added to manufacture the drug product. Testing was performed on the small batches (i.e. ~~performed~~ performed either by the drug substance manufacturer or drug product manufacturer). Based on the information provided by the applicant (lot # and amounts of each batch in a lot) and information provided on catechin components present in each batch, ~~performed~~ performed by the FDA and an acceptance criteria of catechins in the drug substance was proposed based on the amounts contained in clinical batches which were determined to be efficacious. It is deemed that the acceptance criteria of Kunecatechins should be based on the  $\pm$  10% of lower (efficacy) and higher amounts (safety) of each component present in the clinical batches.

---

Signature, minutes preparer

---

Chair concurrence (or designated signatory)

# Attachement



MediGene, Inc.  
10660 Scripps Ranch Blvd., Suite 200  
San Diego, CA 92131 USA  
Tel. (858) 586-2240  
Fax (858) 586-2241  
www.medigene.com

September 14, 2006

Dr. Susan Walker  
Director  
Division of Dermatologic and Dental Products (HFD-540)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705

**RE: New Drug Application # 21-902**

**Polyphenon® E Ointment, 15%**

**Submission No. 038**

**General Correspondence: Meeting Minutes of Teleconference on September 08, 2006 and MediGene's Response to Regulatory Options**

Dear Dr. Walker:

This submission is in response to the teleconference on September 08, 2006. Enclosed, please find MediGene's meeting minutes as Attachment 1 and our response to the regulatory options that have been provided to us. We ask that if the Division does not agree with our summary of the meeting, that we be notified immediately so that our understanding of the Division's position can be clarified.

MediGene is committed to obtain, as soon as possible, a mutually agreeable resolution for the pending New Drug Application (NDA) # 21-902, resulting in approval for Polyphenon® E Ointment, 15%. Consequently, MediGene will not delay the review process by requesting new specifications prior to approval. MediGene, therefore, accepts final product specifications based on drug product used in clinical efficacy studies. It is our understanding that the specifications have been the only remaining major concern from the Agency. As a result, a Type A meeting that was originally requested by MediGene to discuss specifications is withdrawn.

MediGene understands that the drug product specifications proposed by the Division were based solely on Polyphenon® E Ointment, 15%, used in pivotal clinical efficacy studies. However, it was unclear to us during the teleconference if the Division had considered the

other adequate and well-controlled trial, Study CT 1005 (using Polyphenon® E Ointment, 15% batches #592 and #601), in reaching its decision. Study CT 1005 was a Phase 2/3 efficacy trial which also was included in the primary efficacy analysis in the Integrated Summary of Efficacy (ISE). Taking into consideration the Polyphenon® E Ointment, 15% batches used in CT1005, in addition to those used in CT 1017 and CT 1018, and by applying +/- 10% to the minimum and maximum catechin concentration (reference is made to the teleconference on August 01, 2006 where FDA responded to MediGene's request for rationale for setting specifications), the calculated catechin ranges for final drug product are as follows. Data is provided in Attachment 2.

<b>Total Catechins</b>	<b>EGCg</b>	<b>EGC</b>	<b>ECg</b>	<b>EC</b>	<b>Sum of GCg, Cg, GC, C</b>
<b>mg/g</b>	<b>mg/g</b>	<b>mg/g</b>	<b>mg/g</b>	<b>mg/g</b>	<b>mg/g</b>

**Does the Agency agree with these drug product specifications?**

In the meeting held on August 23, 2006 between FDA and the DMF holder (Mitsui Norin), discussion on the specifications for catechins for the drug substance were deferred to the requested Type A meeting that was to be held between FDA and MediGene. Since the Type A meeting request has been withdrawn, discussion of this topic is no longer necessary. For this reason, MediGene would like FDA to confirm that the catechin ranges for Polyphenon® E drug substance are set in a way that enables catechin ranges for the drug product to be achieved and to comply with drug product specifications.

Because the manufacture of Polyphenon® E Ointment, 15% basically is a dispersion of the drug substance in the ointment base, the relative amounts of the individual components (i.e., the relative proportion of catechins) is not changed during manufacture. Therefore, MediGene believes that the upper and lower limits for drug substance should correspond to the ranges in the 15% ointment. The proposed incoming catechin specifications in Polyphenon® E drug substance are as follows:

<b>Total Catechins</b>	<b>EGCg</b>	<b>EGC</b>	<b>ECg</b>	<b>EC</b>	<b>Sum of GCg, Cg, GC, C</b>
<b>% weight</b>	<b>% weight</b>	<b>% weight</b>	<b>% weight</b>	<b>% weight</b>	<b>% weight</b>

The % values are expressed on an anhydrous basis and correspond to the catechin ranges of Polyphenon E Ointment 15% (e.g., a certain catechin with 10% weight in drug substance will correspond to 15 mg of that catechin in 1 g of 15% ointment).

**Does the Agency agree with these drug substance specifications?**

MediGene appreciates the Agency's willingness for an open and constructive dialogue and is looking forward to your response. MediGene is open to discuss, preferably in a face-to-face meeting, the above questions and any remaining topics with you and your staff at your convenience prior to the PDUFA date and the issuance of the action letter.

After approval of the NDA, MediGene would like to continue the discussion with the Division to resolve the issues related to our proposed acceptance criteria for drug product and drug substance specifications which were rejected during this review cycle. Is this approach acceptable to the Division?

Four copies of this submission are provided as outlined below.

- Archive copy – blue vinyl binder
- CMC Copy – red binder
- Clinical copy – tan binder
- Botanical Review Team

If there are any questions regarding this submission or if additional information is needed, please do not hesitate to contact me at (858) 586-2252 or by email at [p.larson@medigeneusa.com](mailto:p.larson@medigeneusa.com).

Sincerely,



Pam Larson  
Sr. Manager, Regulatory Affairs, US  
MediGene, Inc.

cc: Millie Wright, FDA Project Manager DDDDP (desk copy)

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## RESEARCH & DEVELOPMENT

### MEETING MINUTES

**Name of Meeting:** Regulatory Options - FDA Meeting Via Teleconference  
NDA 21-902  
Polyphenon® E Ointment

**Date of Meeting:** September 08, 2006

**Date of Memo:** September 08, 2006

#### Meeting Participants

**FDA:** Dr. Susan Walker, DDDP Director  
Dr. Jill Lindstrom, Lead Medical Officer  
Dr. Elektra Papadopoulos, Medical Officer  
Dr. Shaw Chen, Medical Officer  
Dr. Moo Jhong Rhee, CMC Supervisory Interdisciplinary  
Dr. Rajiv Agarwal, Chemist  
Linda Athey, Regulatory Health Project Manager  
Millie Wright, Project Manager

**MediGene:** K. Jon Kowal, Senior Vice President Research and Development  
Axel Mescheder, Vice President Clinical Research and Development  
  
Paula Stemler, Director Manufacturing  
Klaus Drexler, Senior Director, CMC Chemicals  
Annette Hüttig, Polyphenon® E Project Manager  
Monika Schuetz, Associate Director Regulatory Affairs, EU  
Myleen Ignacio, Regulatory Affairs, U.S.

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The meeting started with introductions of all meeting participants. Dr. Walker then went on to indicate that except for 2 components in our specifications, the specific ranges defined by FDA based on pivotal clinical trial data matches with MediGene's proposed specifications. Dr. Walker then suggested 2 regulatory options for MediGene:

- 1) Approval within this cycle – MediGene has to accept the FDA-proposed specifications in most recent communication (see FDA fax memorandum entitled "CMC Reviewer's Comments for Aug 16<sup>th</sup> Meeting Package" dated August 29, 2006 and FDA-proposed specifications provided in FDA fax memorandum entitled "CMC Information request" dated June 28, 2006)
- 2) Approvable – If MediGene wants approval of specifications outside the FDA-approved specifications, then additional clinical studies covering the broader catechin ranges will need to be conducted as pre-approval commitment

Dr. Kowal inquired with Dr. Walker if FDA would consider all clinical studies to date that demonstrates safety and efficacy. Dr. Walker responded by stating that based on current pivotal clinical information



provided in the NDA, the specifications that have been proposed by FDA are the only specifications FDA would consider. She went on further by saying that if MediGene wanted parameters of specifications other than what was proposed by FDA, then this would result in an approvable letter on the PDUFA date, with the need for additional clinical trials. She stated that FDA will be amenable to having discussions prior to the PDUFA date regarding any list of questions we may have. She did suggest that MediGene send in a list of questions in writing to FDA regarding any inquiries we may have on specifications and/or what was conveyed in this meeting. Dr. Kowal indicated that a pending Type A Meeting was trying to be scheduled and asked if we can provide questions in the briefing package for the Type A Meeting with the Agency to discuss further the specifications. Dr. Walker responded that FDA will not change their minds on the specifications that have been proposed. She stated that a meeting will only be used to discuss other issues outside of the specifications topic since the setting of specifications has already undergone review by the Division.

Dr. Walker indicated that the Agency intends to clarify remaining labeling issues with MediGene soon. Dr. Kowal then inquired to Dr. Walker if there were any deficiencies other than the specifications for our product that will be addressed in the action letter on the PDUFA date. Dr. Walker responded by saying that there are no other informational needs from the Agency except for perhaps some clinical questions that would be considered resolved through a post-market commitment to conduct a Phase 4 study. Dr. Walker provided some insight on what clinical information would be needed such as rates of efficacy for foreign trials versus trials conducted in the United States, however, the parameters of such a study would need to be discussed. A robust Ph IV clinical study would address this issue. Dr. Walker commented that more information on this could be provided by next week.

Dr. Kowal then inquired whether or not FDA will accept the process validation batches' results and stability data with their specifications at CPM. Dr. Agarwal responded that the amount of components in the \_\_\_\_\_ batches are different from CPM, but that FDA will accept the process validation batches and stability data since the problem does not lie in the manufacturing process. Dr. Agarwal stressed that storage at higher temperatures is seen problematic and that the FDA therefore requires storage at 2 to 8 °C because of the observed \_\_\_\_\_ at higher temperatures before dispensing the drug to the patient. Dr. Agarwal therefore requested refrigerated storage and shipment conditions until delivery to the customer. Dr. Walker closed the meeting by restating that should we have any questions, to send these questions in writing to FDA and to deliberate the options provided and inform FDA of our chosen option.

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Attachment 2

Acceptance Criteria for Catechin Ranges in Polyphenon® E Ointment, 15%

Batch Number	Chemical Study	EGCG	EGC	ECg	EC	GCG	Cg	GC	C	Total Catechins	Sum of GCG, Cg, GC, C
		mg/g									
000.402	CT1017										
000.43902	CT1017										
000.10103	CT1018										
592	CT1005										
601	CT1005										
Min											
Max											
Max + 10%											
Min - 10%											

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/s/

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Jill Lindstrom  
10/20/2006 04:46:57 PM

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

6 § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-\_\_\_\_\_

## **FDA Fax Memorandum**

**Date:** October 16, 2006

**Subject:** NDA 21-902/Veregen  
Postmarketing studies (Phase 4s)

Hi Myleen,

Attached are the Agency's requested Phase 4 studies. If needed, once your team has a chance to look at them, we can arrange a t-con to discuss. You will note that for the PK studies, we have proposed dates. If for some reason, the dates proposed are not acceptable to your team, you can make a counterproposal. For the clinical Phase 4, we are requesting that you propose the dates.

Once we reach an agreement on the Phase 4 studies, you will need to submit a letter to the NDA, in which you state the Phase 4s that you have agreed to conduct.

If you have questions, please call me.

Respectfully,  
Millie

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  b   § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-

**DRAFT REVIEWERS' COMMENTS**

**Topic:** NDA 21-902/Veregen  
**Sponsor:** MediGene Inc.  
**Subject:** Briefing document submitted August 16, 2006  
**Meeting Date:** September 13 2006/9:30 AM

**Introductory Comment:** This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 13, 2006, at 1:30 P.M. in White Oak Room 1421 between MediGene the Division of Dermatology and Dental Products, and the Division of Post-Marketing Evaluation. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Millie Wright). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecom). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to [your development plan/the purpose of the meeting/to the questions] (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

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- Will withdraw from the market any batches those are found to fall outside the approved acceptance criteria for the drug product. The change or deterioration in the distributed drug product must be reported under 21CFR 314.81(b)(1).

**Sponsor's Response:**

MediGene suggests performing analysis for future commercial batches on 2 tubes per time point, 1 sample per tube, during long term stability studies at 25°C/60% RH covering the proposed shelf life for the parameters and acceptance criteria indicated in the drug product stability specification. Does the Agency agree to this proposed stability program.

**Agency's Response:**

No. We do not agree with your proposed stability study program.

1. Due to the [redacted] issue, we recommend that the stability program include tubes stored at the [redacted].
2. Based on the [redacted] we recommend you to modify the stability commitment as follows:

1,

- Will withdraw from the market any batches those are found to fall outside the approved acceptance criteria for the drug product. The change or deterioration in the distributed drug product must be reported under 21CFR 314.81(b)(1).
3. The recommended storage for this product will be "Prior to dispensing to the patient, store refrigerated 2°C to 8°C (36°F to 46°F)". Twelve months of shelf life at refrigerated temperature may be granted for your drug product.

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**Question 4:**

Please provide the tabular list of drug product sample and catechin reference standards and an updated finished product specifications for the method validation package.

**Sponsor's Response:**

The method validation package's list of drug product sample, catechins reference standards, and updated finished product specifications will be provided to the agency by September 2006.

**Agency's Response:**

Acceptable

**Question 5:**

The deficiencies related to drug substance specifications were communicated to the DMF holder on **26-JUN-2006**. Please co-ordinate with the DMF holder.

**Sponsor's Response:**

The catechins concentration acceptance criteria were determined using  $\pm 3$  SD from the mean of the individual catechins values from the 63 lots, with the lower being raised to the minimum value in the range of data in those cases where the -3 SD value was less than zero.

**Agency's Response:**

No. The acceptance criteria of catechins proposed by the FDA is based upon the analysis of various lots (quantity of each batch in a lot and assay of each catechin in those batches) of drug substance used to manufacture the drug product batches which was utilized in pivotal clinical trials, and is based on approximately  $\pm 10\%$  of lowest (efficacy) and highest (safety) levels of each component present in the drug product lots. Additionally, the acceptance criteria of GCg that you proposed is very wide and this range was not seen in the clinical batches (15%) to support the safety. Please modify your acceptance criteria to what was proposed by FDA.

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**Project Management**

1. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the NDA might identify additional comments or informational requests.

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/s/

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Susan Walker  
10/13/2006 01:21:54 PM

## FDA Fax Memorandum

**Date:** October 6, 2006  
**Subject:** NDA 21-902/Veregen  
 Clinical Information Request

Hi Myleen,

The clinical reviewer has the following information request regarding the Adverse Events tables provided in the labeling for NDA 21-902. Please submit your response officially and via email to Millie by Tuesday, October 10, 2006.

**Clinical Reviewer's Information Request:**

	Vehicle N=207	Veregen N=397
General Disorders and Administration site Conditions	71	88
Pruritus	56	76
Erythema	37	73
Burning	37	69
Pain	17	56
Ulcer	11	48
Edema	12	44
Induration*	13	36
Desquamation	1	5
Discharge	1	3
Bleeding	1	2
Ulcer		2
Scar		1
Reaction		2
Swelling		<1

Why are there two rows for ulcer? Please explain the difference. Please merge if appropriate and provide rationale (merge or not).

Please merge swelling and edema if they both occurred at the application site.

\*Is induration at the application site?

Please round to whole number and include only percentages in table.

Show in table AEs where incidence is higher in Veregen compared to vehicle (by 1%).

If you have questions, please call.

Respectfully,  
 Margo (for Millie)

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/s/

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Margo Owens  
10/6/2006 05:05:42 PM  
CSO

## **FDA Fax Memorandum**

**Date:** October 4, 2006

**Subject:** NDA 21-902  
CMC Information Request

Hi Myleen,

The following was not included in your September 28, 2006 submission:

1. Please include the specifications of "Appearance" in the "Release specifications for drug product" as proposed in our IR letter.
2. The acceptance criteria of "Appearance" is not provided in the "Stability specifications for drug product".

Please provide the above quickly. Call me and let me know when we can expect your response.

If you have questions, please call me.

Respectfully,  
Millie

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/s/

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Mildred Wright  
10/4/2006 11:41:04 AM  
CSO

## FDA Fax Memorandum

**Date:** October 4, 2006

**Subject:** NDA 21-902  
Label request

Hi Myleen,

As you and I discussed earlier, we are trying to finalize our draft labeling to send to you. We request the following:

- 1) Please provide information for the table 4 below using data from only CT 1018 and CT 1017, the 16-week pivotal studies.

**Table 4: Local Skin Reactions During Treatment**

	Males		Females	
	Veregen™ 15% (N=205)	Vehicle (N=108)	Veregen™ 15% (N=192)	Vehicle (N=89)
Erythema	xx%	xx%	xx%	xx%
Edema	xx%	xx%	xx%	xx%
Induration	xx%	xx%	xx%	xx%
Vesicles	xx%	xx%	xx%	xx%
Erosion/ Ulceration	xx%	xx%	xx%	xx%
Burning	xx%	xx%	xx%	xx%
Itching	xx%	xx%	xx%	xx%
Pain	xx%	xx%	xx%	xx%

- 2) Please provide the following 3 tables with the incidence of all adverse events during treatment by MEDRA Organ Class System and Preferred term using 16-week data from only the two phase 3 pivotal studies (CT1017 and CT1018)
  - a) for all patients (male and female) all adverse events recorded on the local reactions page and adverse events pages of CRF similar to ISS table 12.1.1 but only including studies CT1017 and CT1018;
  - b) for male patients similar to table 12.1.2; and
  - c) for female patients similar to 12.1.3.

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NDA 21-902

If we could receive the following information by no later than COB Thursday, earlier if possible, it would assist us in providing you with the draft label by COB Friday. Please let me know if you can meet our requested Thursday goal date.

If you have questions, please call me.

Respectfully,  
Millie

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/s/

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Mildred Wright  
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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-902

MediGene Inc.

Attention: Myleen Ignacio, M.S., Regulatory Affairs Associate  
10660 Scripps Ranch Blvd., Suite 200  
San Diego, California 92131

Dear Ms. Ignacio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veregen (kunecatechins) Ointment, 15%.

We also refer to the teleconference between representatives of your firm and the FDA on September 8, 2006. The purpose of the teleconference was to discuss the drug product specifications and the drug substance specifications.

The official minutes of that teleconference are enclosed.

If you have any questions, call Millie Wright, Project Manager, at (301) 796-2110.

Sincerely,

*{See appended electronic signature page}*

Susan Walker, M.D.

Division Director

Division of Dermatology and Dental Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Enclosure

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## MEMORANDUM OF TELECON

**DATE:** September 8, 2006

**Application:** NDA 21-902/ Veregen (kunecatechins) Ointment, 15%

**Sponsor:** MediGene, Inc.

**Topic:** Sponsor's submission dated August 16 2006

**FDA Participants:**

**Division Dermatologic and Dental Drug Products/**

Susan Walker, M.D., Division Director

Millie Wright, RN, MSN, Project Manager

**Office of New Drug Quality Assessment II/Division of Pre-Marketing Assessment**

Moo-Jhong Rhee, Ph.D., Branch Chief

Rajiv Agarwal, M.Phil; Ph.D., Ph.D., Reviewing Chemist

Linda Athey, Regulatory Health Project Manager

**Office of Drug Evaluation I**

Shaw T. Chen, M.D., Ph.D. Associate Director & Botanical Team Leader

Jinhui Dou, Ph.D., Botanical Reviewer

**Sponsor Participants:**

Axel Mescheder, MD., Vice President .Clinical Research and Development

Annette Hüttig, Ph.D., Polyphenon<sup>®</sup> E Project Manager

Myleen Ignacio, M.S., Regulatory Affairs Associate II U.S.

K. Jon Kowal, Ph.D., Senior Vice President Research and Development

Paula Stemler, M.S., Director of Manufacturing Operations

Klaus Drexler, Ph.D., Senior Director CMC Chemicals

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**Background**

The Sponsor submitted a meeting requested, August 16, 2006, and an Agency fax, dated August 29, 2006, contained Reviewers' Comments. (See Attachment) Upon receipt of the Reviewers/ Comments, the Sponsor indicated that they still were not in agreement with the Agency.

The Agency requested a t-con with the Sponsor to discuss and clarify their areas of concern.

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**Discussion:**

The Agency began the discussion by acknowledging that agreement had been reached on the acceptance criteria of all but two catechins components (EGCg, ~~GCg~~) present in the product. The acceptance criteria for these two components, EGCg and GCg, proposed by the Sponsor are unacceptable because amounts of these catechins are exceeding the amounts used in the phase 3 pivotal trials. To support the proposed acceptance criteria, the Sponsor was informed that a clinical trial(s) would have to be conducted to establish clinical efficacy and safety using the product with the widened ranges of the components.

The Agency presented the following regulatory options to the Sponsor:

1. The agency has reviewed the information submitted by the applicant as a basis for any regulatory action on this product. This includes the specification ranges for the drug substance used in the clinical trials to establish safety and efficacy. Any approval action would include product specifications consistent with the specifications in the clinical trials, as described by the agency CMC reviewers. The sponsor and agency have agreement on the drug product specifications derived from the batches used in the phase 3 clinical trials. It was noted that the approvability of the NDA could not be made until all of the reviews issues are closed.
2. If the Sponsor wants to use different drug product specifications than those submitted in the NDA, the Agency would require, prior to approval, additional clinical trial(s) conducted with batches containing amounts of the components commensurate with the newly proposed drug product specifications.

The Sponsor voiced their understanding of the regulatory options. They requested a dialogue with the Agency to reach an agreement for different drug product specifications. The Agency expressed a willingness to have dialogue on issues other than specifications, but as far as the issues on the specifications are concerned, the Agency has made their position clear. The Sponsor expressed their desire to continue to pursue an approval action based upon the data currently submitted by the applicant.

The Sponsor inquired if there were other items for discussion which would have an impact on the review of the NDA. The agency noted that there were no informational needs at this time. The Agency reported that we may be requesting a phase 4 study and we would contact them as soon as a determination was made.

Dr. Kowal also inquired whether or not FDA accepts the process validation batches results and stability data conducted at CPM. Dr. Agarwal responded that they are acceptable since the manufacturing processes at CPM and ~~\_\_\_\_\_~~ are comparable; however, he noted that the amounts of catechin components in the ~~\_\_\_\_\_~~ batches are different from those manufactured at CPM and do not correspond to the clinical batches used in pivotal clinical trials. Dr. Agarwal further noted that ~~\_\_\_\_\_~~ in drug product batches manufactured at ~~\_\_\_\_\_~~ or CPM is observed during the stability studies performed at both intermediate and accelerated storage conditions, therefore, the Agency is requiring that the drug product be refrigerated during storage and shipping until being dispensed the patients.

NDA 21-902/ 8 Sept. t-con

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Signature, minutes preparer

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Chair concurrence (or designated signatory)

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/s/

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Mildred Wright  
10/3/2006 08:55:03 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-902

MediGene Inc.

Attention: Myleen Ignacio, M.S., Regulatory Affairs Associate  
10660 Scripps Ranch Blvd., Suite 200  
San Diego, California 92131

Dear Ms. Ignacio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veregen (kunecatechins) Ointment, 15%.

We also refer to the teleconference between representatives of your firm and the FDA on August 1, 2006. The purpose of the teleconference was to discuss the drug product specifications and the drug substance specifications.

The official minutes of that teleconference are enclosed.

If you have any questions, call Millie Wright, Project Manager, at (301) 796-2110.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.

Branch Chief

Division of Pre-Marketing Assessment II

Office of New Drug Quality Assessment

Center for Drug Evaluation and Research

Enclosure

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# MEMORANDUM OF TELECON

**DATE:** August 1, 2006

**Application:** NDA 21-902/ Veregen (kunecatechins) Ointment, 15%

**Sponsor:** MediGene, Inc.

**Topic:** Sponsor's submission dated July, 2006

**FDA Participants:**

**Division Dermatologic and Dental Products/**

Millie Wright, RN, MSN, Project Manager

**Office of New Drug Quality Assessment II/Division of Pre-Marketing Assessment**

Moo-Jhong Rhee, Ph.D., Branch Chief

Rajiv Agarwal, M.Phil; Ph.D., Ph.D. Reviewing Chemist

**Sponsor Participants:**

Irene Gander-Meisterernst, Ph.D., Sr. Director Regulatory Affairs

Annette Hüttig, Ph.D., Polyphenon<sup>®</sup> E Project Manager

Myleen Ignacio, M.S., Regulatory Affairs Associate II U.S.

K. Jon Kowal, Ph.D., Senior Vice President Research and Development

Paula Stemler, M.S., Director of Manufacturing Operations

Klaus Drexler, Ph.D., Senior Director CMC Chemicals

Ira Peine, MediGene US Representative to Mitsui Norin Co., Ltd.

**Background**

In their July 11, 2006 submission, MediGene requested a t-con to discuss the following:

“To ensure that MediGene responds appropriately and accurately to the fax memorandum entitled “CMC Information Request”, dated June 2006, MediGene hereby formally requests the Agency’s general view and rationale for the proposed finished product specifications and acceptance criteria (release and stability) for Assay: Catechins. Additionally, we have reviewed the drug substance specifications, which were communicate in a letter to our DMF — holder, Mitsui Norin Co. Ltd, on June 26, 2006 and also request the rationale and justification made by FDA for the catechin specifications in the drug substance.” (See Attachment for copy of fax.)

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**Discussion:**

The Agency began the discussion by explaining that this botanical NDA, has not demonstrated that what is the active component/components in the botanical drug substance. Therefore, the whole drug substance is considered active. Therefore, in order to establish meaningful specifications, we focused on the amount of each component in the pivotal clinical batches and determined the amount of each component virtually calculated based on the information on the amount of drug substance batch added for formulating the clinical batches. Once we know the highest amount of the component in the clinical batch, we allowed an extra +10% and we did the same thing (-10%) for the lowest amount of the same component. Therefore, to meet the specifications, \_\_\_\_\_ may have to be done.

The Sponsor expressed concern that this is extremely difficult and inquired if the Agency would consider other batches besides the ones used in the clinical trials. When asked if they had established efficacy with the other batches, the Sponsor responded that they had not.

The Agency stressed that the specifications for both the drug substance and the drug product must be derived from the clinical batches proven to be efficacious.

Discussion ended.

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Signature, minutes preparer

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Chair concurrence (or designated signatory)

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# FDA Fax Memorandum

**Date:** June 28, 2006

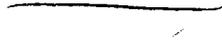
**Subject:** NDA 21-902  
CMC Information Request

Hi Pam,

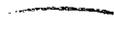
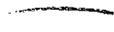
The CMC reviewer has the following information request:

1. Please revise the finished drug product specifications and acceptance criteria for Appearance and Assay of catechins. Also expand specifications to include acceptance criteria for gallic acid, particle size of polyphenon E, oleyl alcohol and viscosity as follows:

Tests	Analytical procedure	Specifications
Appearance	Visual inspection	1
Identification: EGCg	—	Retention time ( $t_R$ ) of sample peak for EGCg does not deviate by more than $\pm 2.0\%$ from corresponding standard run.
Identification: Catechins		Relative Retention Time to EGCg
EC		
ECg		
GCg		
EGC	—	
GC		
Cg		
C		
Assay: Catechins		
EGCg		
EC		
EGC	—	
ECg		
Total minor catechins (GCg, Cg, GC, and C)		
Total catechin content		
Gallic Acid	Please provide method #	
Particle size of Polyphenon E	Please provide	Please provide
Oleyl alcohol	Please provide	Please provide

<b>Viscosity</b>	<b>Please provide</b>	<b>Please provide</b>
Microbial limit	USP <61>, EP 2.6.12, EP 2.6.13	
Minimum Fill	USP <755>	Net weight mean of 10 tubes NLT labeled amount Net weight of 10 individual tubes NLT of labeled amount

2. Please revise the drug product stability specifications and include the acceptance criteria for gallic acid and particle size of polyphenon E and revise the acceptance criteria of assay of catechins as follows:

Tests	Analytical procedure	Specifications
Appearance	Visual inspection	
Appearance (tube)	Please provide	<b>Tubes are intact and no material leakage is visible. No damage of the inner lacquer.</b>
Identification: EGCg		Retention time ( $t_R$ ) of sample peak for EGCg does not deviate by more than $\pm 2.0\%$ from corresponding standard run.
Identification: Catechins		
EC		
ECg		
GCg		
EGC		
GC		
Cg		
C		
Assay: Catechins		
EGCg		
EC		
EGC		
ECg		
Total minor catechins (GCg, Cg, GC, and C)		
Total catechin content		
<b>Gallic acid</b>	<b>Please provide</b>	<b>Please provide</b>

<p>Rheology: Viscosity and yield Value</p>	<p>EP 2.2.8, USP &lt;911&gt;</p>	 <p><i>Yield Value=</i></p>
<p>Consistency</p>	<p>Penetrometry, EP 2.9.9</p>	
<p><b>Particle size (Drug substance)</b></p>	<p><b>Please provide</b></p>	<p><b>Please provide</b></p>
<p>Microbial limit</p>	<p>USP &lt;61&gt;, EP 2.6.12, EP 2.6.13</p>	

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3. Please revise the stability commitment as follows:

- 
- Will withdraw from the market any batches those are found to fall outside the approved acceptance criteria for the drug product. The change or deterioration in the distributed drug product must be reported under 21CFR 314.81(b)(1).
4. Please provide the tabular list of drug product sample and catechin reference standards and an updated finished product specifications for the method validation package.
  5. The deficiencies related to drug substance specifications were communicated to the DMF holder on 26-JUN-2006. Please co-ordinate with the DMF holder.

If you have questions, please call me.

Respectfully,  
Millie

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/s/

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Moo-Jhong Rhee  
10/2/2006 09:47:55 AM  
Chief, Branch III

1 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

1 § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-*

I am working on a fax, which contains changes to the CMC, Pharm/tox and PK sections of the labeling. As discussed with you earlier in the week, the clinical/stat sections of the label are still being revised.

I did not want to delay sending the comments for the carton and container labeling, since I am aware that it will take you longer to implement the changes. The changes to the carton and container labeling should be submitted as a colored mock up.

Please call me next week and let me know when to expect the submission. If you have questions, please call me.

Respectfully,  
Millie

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/s/

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Mildred Wright  
9/29/2006 03:59:40 PM  
CSO

7 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(4) Draft Labeling

4 § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-\_\_\_\_\_



Felix Grigorian, M.D., Ph.D.  
City Clinical Hospital Number 13  
Department of Gynecology  
Velozavodskaya st., 1/1  
109280  
Moscow, Russia

Dear Dr. Grigorian:

Between May 15 and 19, 2006, Dr. Gerald McGirl, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation (protocol CT1017 entitled "A Randomized, Double-Blind, Three-Arm Parallel-Group, Placebo-Controlled Phase 3 Trial to Investigate the Clinical Efficacy and Safety of Polyphenon<sup>®</sup> E in the Treatment of External Genital Warts") of the investigational drug Polyphenon<sup>®</sup> E, performed for Medigene AG.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Dr. McGirl during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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/s/

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Constance Lewin  
7/5/2006 03:29:47 PM



Ester A. Santander, M.D.  
Hospital San Jose CDT Dra Eloisa Diaz  
Profesor Zanartu 1085  
Independencia  
Santiago, Chile

Dear Dr. Santander:

Between May 22 and 26, 2006, Dr. Gerald McGirl, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation [protocol CT1018 entitled "A Randomized, Double-Blind, Three-Arm Parallel-Group, Placebo-Controlled Phase 3 Trial to Investigate the Clinical Efficacy and Safety of Polyphenon® E in the Treatment of External Genital Warts"] of the investigational drug Polyphenon® E, performed for Medigene AG.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Dr. McGirl during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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/s/

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Constance Lewin

7/5/2006 03:14:02 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-902

MediGene, Inc.  
Attention: Pam Larson  
Sr. Manager, Regulatory Affairs  
10660 Scripps Ranch Blvd. Suite 200  
San Diego, CA 92131  
USA

Dear Ms. Larson:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for polyphenon E ointment.

On May 30, 2006, we received your May 26, 2006, major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 31, 2006.

If you have any questions, call Millie Wright, Project Manager, at (301) 796-2110.

Sincerely,

*{See appended electronic signature page}*

Susan Walker, M.D.  
Division Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Susan Walker  
6/26/2006 04:45:27 PM



James Swinehart, M.D.  
950 E. Harvard Avenue, #630  
Denver Colorado 80210-7002

Dear Dr. Swinehart:

Between March 21 and 28, 2006, Ms. Linda Cherry, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation (protocol CT1018 entitled "A Randomized, Double-Blind, Three-Arm Parallel-Group, Placebo-Controlled Phase 3 trial to Investigate the Clinical Efficacy and Safety of Polyphenon<sup>®</sup> E in the Treatment of External Genital Warts") of the investigational drug Polyphenon<sup>®</sup> E, performed for Medigene AG.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your March 31, 2006, letter written in response to the Form FDA 483, Inspectional Observations, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We are aware that at the conclusion of the inspection, Ms. Cherry presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
  - a. The protocol specified that screening blood samples were to be drawn for hematology and chemistry analyses and that these analyses were to be reviewed for any exclusionary values prior to subject study enrollment; however, subject 0979 was enrolled into the study without review of these screening laboratory results.
  - b. The protocol specified that screening laboratory blood samples be analyzed for gamma-glutamyl transferase (GGT) levels; however, this specific laboratory analysis was not done for subjects 0976, 0977, and 0978.

James Swinehart, M.D.

We appreciate the cooperation shown Investigator Cherry during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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/s/

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Constance Lewin  
6/22/2006 03:40:42 PM

3 Page(s) Withheld

6 § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-\_\_\_\_\_*

## FDA Fax Memorandum

**Date:** May 22, 2006

**Subject:** NDA 21-902  
CMC Information Request

Hi Pam,

The CMC reviewer has the following information request:

1. Provide the pH of the clinical trial and primary stability drug product batches for both the 10% and 15% strengths.
2. Provide a detailed description of the tube filling process.

If you have questions, please call me.

Respectfully,  
Millie

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/s/

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Mildred Wright  
5/22/2006 01:37:14 PM  
CSO

## FDA Fax Memorandum

**Date:** May 22, 2006

**Subject:** NDA 21-902  
T-con Agenda

Hi Pam,

We will be discussing the following:

1. The Agency could not reproduce the sponsor's efficacy results neither from the original data or the other data sets which the sponsor submitted on 1/6/06 and 3/6/06 in response to the Agency requests. The sponsor should identify the data set used to generate the efficacy results and provide the Agency with the program code used for such analysis. It should be noted that analysis should be carried out for the protocol-specified population (ITT population).
2. Concerning the relapse data for subjects who were cleared it appears that the sponsor used the same notation for missing data as well as for '0' count of warts. With such possibility of dual use of the same notation it is difficult to calculate the relapse rate and reproduce the sponsor's results. Sponsor is requested to provide data set which delineate between the missing data and the '0' counts along with computer program which generated their relapse results.

As you and I discussed earlier, I have time scheduled for 4:30 PM tomorrow (5/23). However, due to fact that your colleagues in Germany have already left for the day, you can't confirm until Tuesday morning that they will be available. For that reason, I have schedule a back-up time for Wednesday ((5/24) at 3:00 PM. Call me in the AM and I will let the team know when the t-con will occur.

If you have questions, please call me.

Respectfully,  
Millie

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/s/  
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Mildred Wright  
5/22/2006 02:29:44 PM  
CSO

## FDA Fax Memorandum

**Date:** April 6, 2006  
**Subject:** NDA 21-902  
Information Request

Hi Pam,

The clinical reviewer has the following request regarding your NDA 21-902:

**Clinical Reviewer's Information Request:**

1. Provide one sample of the placebo and drug product that were used in the clinical trials.
2. Provide three samples of the to-be-marketed product.

Please send the samples as soon as possible to the following address:

Mildred Wright  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Building 22, Room 5152  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

If you have questions, please call.

Margo Owens (for Millie Wright)

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/s/

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Margo Owens  
4/6/2006 04:12:40 PM  
CSO

## FDA Fax Memorandum

**Date:** March 1, 2006

**Subject:** NDA 21-902  
Information Requests

Hi Pam,

The reviewers have the following requests:

### Clinical Pharmacology/CMC

The drug product used in the PK studies and Phase 3 clinical trials was manufactured by \_\_\_\_\_. The proposed commercial manufacturer is CPM. This will result in a change in the pharmacopoeial grade of the white petrolatum, cera alba and oleyl alcohol from USP and NF to EP. It will also result in a change in some of the manufacturing process parameters.

On page 34 of Module 2.3 in Volume 1, the sponsor claims that based on the in vitro release studies and the other studies evaluating the physicochemical characteristics of the Polyphenon E Ointment, 15% they can conclude that the product produced at CPM is comparable to the product used in Phase III clinical studies. A preliminary evaluation of the in vitro release data provided on the same page suggests that, the product produced at \_\_\_\_\_ (Batch No. B000.10103, manufactured in May 2003) had a different release profile from the product manufactured at CPM Contract Pharma (Batch No. 39075-1, manufactured in September, 2004). This implies that the product produced at CPM may not be comparable to the product used in the Phase III clinical studies and the PK study. Therefore the in vitro release data as presented may not be adequate to support comparability between the product produced at \_\_\_\_\_ and that produced at CPM.

Do you have any other data that may be used to support the comparability of the two drug products? Also please clarify whether your conclusion on the comparability of the in vitro release tests was based on any kind of statistical analysis.

**Clinical:**

In your February 22, 2006 e-mail you requested the following clarification regarding Clinical question # 7 in the fax from FDA dated February 1, 2006.

Question 7 states, "As a reviewer aid, please provide for the clinical module (M) a table of contents according to volume number and page number as well as section number."

This can be done, however, the page number reference will refer to page 1 in most instances since according to the Common Technical Document (CTD) format, each section is independently page numbered. Navigation of the paper CTD is intended to be done with the binder tabs. Therefore, each new section is immediately preceded by an identifying tab and the document within the section is numbered beginning with page 1. The table of contents currently provided with our original NDA submission provides the volume number and tab identifier as recommended for the CTD format. The tab identifier contains the CTD section number as well as some additional identifying information such as the applicable report number.

MediGene can provide a reviewer aid as requested with page numbers, however, as indicated previously, we do not feel that it would be much more helpful since all of the section page references would indicate page 1. Can you please check with the applicable clinical reviewer if a reviewers aid with page numbers is still needed?

**Reviewer's Response:**

Attached are the portions of the table of content for the clinical study reports that lack volume numbers. Please provide volume numbers by each of the sections so that the correct volume can easily be found.

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Document Type	Study No.	Version:
Clinical Study Report	CT 1017	V02 Final
Short Title		
Clinical Efficacy of Polyphenon® E in the Treatment of External Genital Warts		

16. Appendices.....16.1-16.4

16.1 Study Information

- 16.1.1 Protocol and Protocol Amendments
- 16.1.2 Sample Case Report Form
- 16.1.3 List of IECs and Sample Written Information for Patient and Sample Consent Forms
- 16.1.4 List and Description of Investigators and other Important Participants in the Study, including CVs
- 16.1.5 Signatures of Principal or Coordinating Investigators or Sponsor's Responsible Medical Officer
- 16.1.6 Listing of Patients Receiving Test Drug from Specific Batches, when more than one Batch was used; Certificates of Analysis
- 16.1.7 Randomization Scheme and Codes
- 16.1.8 Audit Certificate
- 16.1.9 Documentation of Statistical Methods
- 16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures if used
- 16.1.11 Publications Based on the Study
- 16.1.12 Important Publications Referenced in the Report

16.2 Patient Data Listings

- 16.2.1 Discontinued Patients
- 16.2.2 Protocol Deviations
- 16.2.3 Patients Excluded from the Efficacy Analysis
- 16.2.4 Demographic Data
- 16.2.5 Compliance and/or Drug Concentration Data (if available)
- 16.2.6 Individual Efficacy Response Data
- 16.2.7 Adverse Event Listings (each patient)
- 16.2.8 Listing of Individual Laboratory Measurements by Patient (if required)

16.3 Case Report Forms

- 16.3.1 CRFs of deaths, other Serious Adverse Events and Withdrawals for Adverse Events
- 16.3.2 Other CRFs submitted

16.4 Individual Patient Data Listings (US Studies Only)

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Document type	Study no.	Version:
Clinical Study Report	CT 1018	V02 Final
Short Title		
Clinical Efficacy of Polyphenon® E in the Treatment of External Genital Warts		

6. Appendices.....16.1-1

16.1 Study Information

- 16.1.1 Protocol and Protocol Amendments
- 16.1.2 Sample Case Report Form
- 16.1.3 List of IECs and Sample Written Information for Patient and Sample Consent Forms
- 16.1.4 List and Description of Investigators and other Important Participants in the Study, including CVs
- 16.1.5 Signatures of Principal or Coordinating Investigators or Sponsor's Responsible Medical Officer
- 16.1.6 Listing of Patients Receiving Test Drug from Specific Batches, when more than one Batch was used; Certificates of Analysis
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- 16.1.8 Audit Certificate
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16.3 Case Report Forms

- 16.3.1 CRFs of deaths, other Serious Adverse Events and Withdrawals for Adverse Events
- 16.3.2 Other CRFs submitted

16.4 Individual Patient Data Listings

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Please let me know when you will submit your response to our February 1<sup>st</sup> fax.

If you have questions, please call me.

Respectfully,  
Millie

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/s/

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Mildred Wright  
3/1/2006 04:30:55 PM  
CSO

## Hummel, Robert

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**From:** Hummel, Robert  
**Sent:** Wednesday, February 22, 2006 4:14 PM  
**To:** 'Pam Larson'  
**Subject:** NDA 21-902

Pam,

Please provide the unit composition, information on drug substance batches (sub and master batch numbers, composition of individual components in sub batches, and quantity of each sub batch in master drug substance batch), and manufacturer of the drug product batches 000.38402, B000.09903, 000.43902, and 00038402 used in clinical studies CT1017 and CT1018.

Thanks,

Bob

Robert L. Hummel, Sr., DBA, RAC  
Regulatory Health Project Manager  
Division of Premarketing Assessment II  
Office of New Drug Quality Assessment  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, MS-2411  
White Oak Building #22, Room 2483  
Silver Spring, MD 20993-0002  
Tel: 301-796-1981  
Fax: 301-796-9850  
[robert.hummel@fda.hhs.gov](mailto:robert.hummel@fda.hhs.gov)

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/s/

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Robert Hummel  
2/24/2006 05:53:21 PM

## FDA Fax Memorandum

**Date:** February 1, 2006

**Subject:** NDA 21-902  
Clinical/Statistical Information Requests

Hi Pam,

The clinical and statistical reviewers have the following requests:

**Statistical:**

In the original NDA, the data sets referenced by the data definition file contained only derived data (i.e. after imputation of missing data). On December 8, 2005 the Agency requested raw data files (i.e. prior to imputation of missing data). The sponsor's response to the Agency's request on January 6, 2006 contains two folders CT1017m and CT1018m with raw data files. However, the format and names of these data sets differ from the data sets in the original submission, which are the only data sets with a corresponding data definition file. To facilitate the NDA review please provide data sets which contain raw data (prior to imputation) for each of the pivotal studies CT1017 and CT1018 using the format similar to the example data below.

In the case the data is missing, these cells of the data should be shown as NA. The sponsor should note that every individual subject should have 12 rows of data (i.e. visit 0 – 11) regardless if subjects attended the visit. In this dataset the OPID, visit, site, and trt columns never have missing data. The definition of each visit is as follows: 0=screening, 1=baseline, 2=week two, 3=week four, 4=week six, 5=week eight, 6=week ten, 7=week twelve, 8=week fourteen, 9=week sixteen, 10=four week after treatment follow-up, and 11=twelve week after treatment follow-up.

In addition to the data sets shown below, data sets should be submitted in a similar format for local safety variables. This should include both investigator and patient assessments of local safety. Again, each subject should have 12 rows of data corresponding to up to 12 visits as described in the paragraph above.

Note that the ITT flag included in the data set should correspond to the protocol defined ITT population of all subjects randomized to treatment as was agreed upon with the Division. The sponsor should note that the ITT populations provided in the Study Reports (i.e. efficacy-analyzable and 16-week completers) do not correspond to the definition in the protocol and as such will be not be considered as the primary analysis population.

Further, can the sponsor please clarify that subjects with ID numbers 15xxx are screening failures in Study CT1018? If so, please submit information on the reason for screening failure and not being randomized to treatment.

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OPID	visit	site	trt	date	Number warts	Area warts	New warts (Y/N)	Number New warts	100% Clear (Y/N)	ITT Flag	PP Flag
CT1018 ARG-01 00101	0	ARG-01	Oint10								
CT1018 ARG-01 00101	1	ARG-01	Oint10								
.	.	.	.								
CT1018 ARG-01 00101	10	ARG-01	Oint10								
CT1018 ARG-01 00101	11	ARG-01	Oint10								
CT1018 ARG-01 00102	0	ARG-01	Vehicle								
CT1018 ARG-01 00102	1	ARG-01	Vehicle								
.	.	.	.								
CT1018 ARG-01 00102	10	ARG-01	Vehicle								
CT1018 ARG-01 00102	11	ARG-01	Vehicle								
.	.	.	.								
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**Clinical:**

1. A high number of subjects (64) in Study CT 1018 withdrew consent prior to randomization. The reasons for withdrawal of consent are not discussed in the study report. Please provide the subject numbers and sites for these subjects as well as reasons for withdrawal. If this information is already provided, please inform us where this can be located in the submission.
2. The study reports for both phase 3 studies, lists withdrawal of consent as a common reason listed for early discontinuation after randomization. Please provide reasons for withdrawal of consent for these subjects also. Did any of these subjects report adverse events and if so, what were the adverse events reported?
3. A study site in Romania, site 5, had efficacy findings reversed in both clinical studies with all patients receiving vehicle ointment (4 in each study) showing complete clearance of warts. Also, the site had a relatively low adverse event incidence. No adverse events were reported for study CT1017 and very few were reported for CT1018. Please provide any information that could explain these findings.
4. Please comment on definitions of the ITT populations in studies CT 1017 and CT 1018 and on why some subjects were excluded from the primary analysis of Study CT 1018. (See statistical comment above.)

5. Subjects who had clearance of all external genital and perianal warts prior to week 16 of study treatment went into the follow-up phase of the clinical trial. How many subjects in each trial fall into this category? Of these subjects, please summarize the clinical outcomes in terms of how many remained wart-free.
6. Several subjects suffered from local adverse events described as erosive or vesicular in nature. Was an evaluation done for potential herpetic infections, either primary or reactivation? What was the extent of screening for sexually transmitted diseases in these subjects and in the overall population enrolled in the pivotal trials?
7. As a reviewer aid, please provide for the clinical module (M) a table of contents according to volume number and page number as well as section number.

If you have questions, please call me.

Respectfully,  
Millie

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/s/

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Mildred Wright  
2/1/2006 06:00:05 PM  
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SEP 6 2005

Ms. Pam Larson  
Sr. Manager, Regulatory Affairs  
MediGene, Inc.  
10660 Scripps Ranch Blvd., Suite 200  
San Diego, CA 92131

**RE: MediGene AG, Small Business Waiver Request 2005.046 for NDA 21-902**

Dear Ms. Larson:

This responds to the May 11, 2005, letter from Becky Donahue, MediGene, Inc., and your June 24, 2005, amendment on behalf of MediGene AG (MediGene) requesting a waiver of the human drug application fee for new drug application (NDA) 21-902, Polyphenon E, under the small business waiver provision, section 736(d)(1)(D)<sup>1</sup> of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2005.046). For the reasons described below, the Food and Drug Administration (FDA) grants the MediGene request for a small business waiver of the application fee for NDA 21-902, Polyphenon E.

According to your letter, MediGene and its affiliates combined have fewer than 500 employees. Additionally, you stated that MediGene AG does not have any prescription drug products introduced or delivered for introduction into interstate commerce in the United States and does not expect to introduce a prescription drug product into the United States within the next 12 months. You also noted that you plan to submit your NDA 21-902 to the Agency in mid- to late September 2005. There was one affiliate identified in the waiver request, MediGene, Inc.

Under section 736(d)(3) of the Act,<sup>2</sup> a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate<sup>3</sup> submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

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<sup>1</sup> 21 U.S.C. 379h(d)(1)(D).

<sup>2</sup> 21 U.S.C. 379h(d)(3).

<sup>3</sup> "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

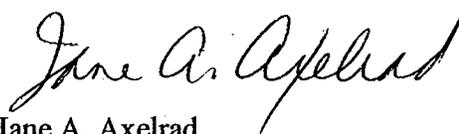
FDA's decision to grant MediGene's request for a small business waiver for NDA 21-902 is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated August 15, 2005, that MediGene and its affiliates, MediGene, Inc., MediGene Oncology GmbH, LARNAX GmbH, Munich Biotech, AG, and Freitag & Co., have fewer than 500 employees. Second, according to FDA records, the marketing application for NDA 21-902 is the first human drug application, within the meaning of the Act, to be submitted to FDA by MediGene or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 21-902, Polyphenon E, is granted, provided that FDA receives the marketing application for the NDA no later than August 15, 2006, 1 year after the effective date of the size determination made by SBA.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for MediGene's NDA 21-902, Polyphenon E. FDA records show that MediGene has not submitted NDA 21-902. If FDA refuses to file the application or MediGene withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, MediGene should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,



Jane A. Axelrad  
Associate Director for Policy  
Center for Drug Evaluation and Research

BCC:

HFD-5 M. Jones

HFD-7 B. Friedman

HFD-7 Chron file

HFD-5 MediGene waiver file

HFD-540 Project Manager for NDA 21-902

HFM-110 C. Vincent/R. Eastep

HFA-100 M. Louviere, P. Joseph

HFA-103 K. Boyd (

HF-20 F. Claunts

HFV-3 T. Forfa

HFV-100 D. Newkirk

Drafted: B. Friedman 8/26/2005

CDER Application Check: 8/26/2005

CBER Application Check: C. Vincent: 8/26/2005

Edited: S. O'Malley 8/30/2005

Reviewed and Signed: J. Axelrad 9/5/2005

Date: 9/6/2005

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14 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-\_\_\_\_\_*



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-902

MediGene, Inc.  
Attention: Pam Larson  
Sr. Manager, Regulatory Affairs  
10660 Scripps Ranch Blvd., Suite 200  
San Diego, California 92131

Dear Ms. Larson:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polyphenon E Ointment, 15%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 29, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry, Manufacturing and Controls

1. Inconsistency in drug product specification is noted between the specification provided on p. 1 of 4 in Section 3.2.P.5 and that provided on p. 54 of 81 in Module 2.3 Quality Overall Summary.
2. The identity and the assay of the penetration enhancer, oleyl alcohol, are not included in the proposed drug product specification.
3. No information is provided for the characteristics (size, nature, and solid structure) of drug substance particles and the particles present in the proposed drug product although a request for information was made regarding this in the pre-NDA meeting dated January 24, 2005.
4. In your September 23, 2005, submission, you inform the Agency that the botanical drug substance manufacturer, Mitusi Norin Co., Ltd., has applied for an International Non-Propriety Name (INN) for the active moiety Polyphenon E through the World Health Organization. You further state that this application is still pending.
5. Although labeling text is provided, container labels can not be found.
6. It is unclear which formulation is used in the pharmacokinetic studies.

7. We note your commitment in your September 23, 2005, submission to submit additional stability data in December 2005, to support a longer shelf life. The additional stability data has not been submitted. The updated stability data will facilitate the CMC review.

Clinical Pharmacology and Biopharmaceutics

1. For study #CT 1007, we noticed that the Binomial Scientific Name for the plant (*Camellia sinensis* O. Ktze) used for the brewed green tea "control" treatment arm is different from that used as the botanical raw material (*Camellia sinensi* (L.) O. Kuntze) for the Polypenon E Ointment, 15%, used in the same study.

Statistical

1. We were able to locate data which includes imputed values, but were not able to locate the original data (i.e. before imputation) for studies CT1017 and CT1018. It should be noted that without having the original data (i.e. prior to imputation) it might be difficult to reach a conclusion about efficacy.
2. No allocation lists of subjects to treatment prior to study enrollment was provided.
3. Only 10% of subjects enrolled in Study CT1018 were from United States (U.S.) sites and no U.S. sites were included in Study CT1017.

Clinical

1. The following observations have raised questions about the generalizability of the submitted clinical data to the broader U.S. population with external genital warts.
  - a. Of the two pivotal studies submitted in the NDA, Study CT107 was done exclusively outside the U.S. Study CT1018 included investigational sites within the US. The proportions of responders in both vehicle and active study arms were notably lower in the U. S., as a whole, compared with the other participating countries.
  - b. You also state on the first page of the introduction to the clinical study report for Study CT1018, "Two studies conducted in the USA and Canada with Polyphenon E 15% ointment failed to show the efficacy of the Chinese study." It is not clear which studies (Chinese or US) are being referred to in this statement.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Chemistry, Manufacturing and Controls

1. Please clarify which set of drug product specification is correct.
2. Please revise the proposed drug product specification by adding specifications for the identity and assay of \_\_\_\_\_ oleyl alcohol.
3. Please provide information for the characteristics (size, nature, and solid structure) of the particles for both bulk drug substance and drug product.
4. Please update the Agency for the status of the application for International Non-Proprietary Name (INN).
5. Please provide electronic copies, colored, mock-ups, of the container/carton labeling for review.
6. Provide formulation compositions for all the pharmacokinetic studies.
7. Please inform the Agency if you no longer plan on submitting the additional stability data in December 2005. However if you still plan on submitting additional stability data to support a longer shelf life, please provide the projected submission date.

Clinical Pharmacology and Biopharmaceutics

1. Please clarify whether this difference in names means that they are from different sources.

Statistical

1. If original data sets were submitted, please provide name and location of the data set(s). Otherwise please submit the original data set(s).
2. Please provide treatment allocation list which show allocation of subjects to treatment prior to study enrollment as well as actual treatment allocation and any deviation of actual location from the treatment allocation list.
3. Please provide study information for the two studies referred to in the statement from the clinical study report for CT1018, "Two studies conducted in the USA and Canada with Polyphenon E 15% ointment failed to show the efficacy of the Chinese study." Such information should include protocols and data sets which include baseline and demographic data along with safety and efficacy data. The data should be provided prior to imputation of missing data as well as after imputation.

Clinical

1. Please submit supportive information regarding the generalizability of the clinical data in the NDA package to the United States population with external genital and perianal warts. The supportive information should:
  - a. Address population characteristics that may affect clinical outcome as well as potential geographic differences among HPV strains that may lead to differences in treatment effect. Please also address whether any biopsies for typing of HPV strains were taken in any of the clinical studies.
  - b. Clarify the statement on the first page of the introduction to the clinical study report for Study CT1018 that states, "Two studies conducted in the USA and Canada with Polyphenon E 15% ointment failed to show the efficacy of the Chinese study."

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Millie Wright, Project Manager, at (301) 796-2110.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Acting Division Director  
Division of Dermatology and Dental  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Jill Lindstrom  
12/8/2005 02:45:50 PM  
Signed on behalf of Stanka Kukich, MD

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 21-902

Supplement #

Efficacy Supplement Type SE-

Trade Name: Polyphenon E Ointment

Established Name: To be determined

Strengths: 15%

Applicant: MediGene

Agent for Applicant: Pam Larson, Sr. Manager, Regulatory Affairs

Date of Application: September 23, 2005

Date of Receipt: September 30, 2005

Date clock started after UN: N/A

Date of Filing Meeting: November 19, 2005

Filing Date: December 13, 2005

Action Goal Date (optional):

User Fee Goal Date: July 28, 2006 (30<sup>th</sup> is on Sunday)

Indication(s) requested: The topical treatment of external genital and perianal warts (*Condylomata acuminata*) in adult patients.

Type of Original NDA: (b)(1)  (b)(2)   
OR  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

- (1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*
- (2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

NDA is a (b)(1) application      OR       NDA is a (b)(2) application

Therapeutic Classification: S  P   
Resubmission after withdrawal? N/A Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 1  
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity*

Version: 12/15/2004

*This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.*

or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES  NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? N/A YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO

- Was form 356h included with an authorized signature? YES  NO

**If foreign applicant, both the applicant and the U.S. agent must sign.**

Sponsor requested to submit signed 356H, only agent submitted 356H

- Submission complete as required under 21 CFR 314.50? YES  NO

If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A  YES  NO

**If an electronic NDA, all forms and certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A  YES  NO

- Is it an electronic CTD (eCTD)? N/A  YES  NO

**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES  NO

- Patent information submitted on form FDA 3542a? YES  NO

- Exclusivity requested? YES, X Years NO   
(5  
year)

**NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES X NO   
**(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
**NOTE:** Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y X NO

- PDUFA and Action Goal dates correct in COMIS? YES X NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 56,401

- End-of-Phase 2 Meeting(s)? Date(s) November 11, 2001 NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 24, 2005 NO   
If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic "Content of Labeling" submitted? YES X NO   
If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES X NO

- Risk Management Plan consulted to ODS/IO? N/A X YES  NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y X NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES X NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A  YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES  NO
  - Has DOTCDP been notified of the OTC switch application? N/A  YES  NO
- YES

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A  YES  NO
- YES

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO
  - If no, did applicant submit a complete environmental assessment? YES  NO
  - If EA submitted, consulted to Florian Zielinski (HFD-357)? YES  NO
  - Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
  - a parenteral product, consulted to Microbiology Team (HFD-805)? N/A YES  NO
- The CMC reviewer is contacting the Sponsor to inquire about the EA and categorical exclusion.  
Could not find it in the submission.

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: November 19, 2005

BACKGROUND: Polpyphenon E Ointment, NDA 21-902, is a NME which is indicated for the treatment of external genital and perianal warts in adult patients. Polpyphenon E ointment, 15% contains a botanical drug substance derived from green tea leave of *Camellia sinensis*. The proposed pharmacologic class is an immuno-modulatory

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>	<u>Review Date</u>
Medical:	E. Papadopoulos	May 30, 2006
Secondary Medical:	N/A	
Statistical:	Mat Soukup	May 15, 2006
Pharmacology:	J. Yao	May 30, 2006
Statistical Pharmacology:	N/A	
Chemistry:	R. Agarwal	May 30, 2006
Environmental Assessment (if needed):		
Biopharmaceutical:	A. Adebawale	May 30, 2006
Microbiology, sterility:	N/A	
Microbiology, clinical (for antimicrobial products only):	N/A	
DSI:	Roy Blay	TBD
Regulatory Project Management:	Millie Wright	
Other Consults:	Botanical Team Shaw Chen Jinhui Dou Leslie Vaccari	April 30, 2006

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site inspection needed? YES  NO
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
• Biopharm. inspection needed?			YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
PHARMACOLOGY	N/A	<input type="checkbox"/>	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
• GLP inspection needed?			YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
CHEMISTRY	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
• Establishment(s) ready for inspection?			YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
• Microbiology			YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. (December 13, 2006)

**ACTION ITEMS:**

1.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3.  Convey document filing issues/no filing issues to applicant by Day 74, December 13, 2005.

Millie Wright  
Regulatory Project Manager,  
Division of Dermatology and Dental Products

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this page is the manifestation of the electronic signature.**  
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/s/

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Mildred Wright  
1/31/2006 01:06:51 PM  
CSO

Mary Jean Kozma Fornaro  
2/1/2006 02:30:01 PM  
CSO  
This is a 505(b)(1) application.